Endothelial dysfunction in heart failure and potential for reversal by ACE inhibition

Helmut Drexler

One of the main clinical symptoms of chronic heart failure is early fatigue during physical activity, which has been linked to impaired perfusion of skeletal muscle during exercise. In patients with chronic heart failure the increase in blood flow to working muscle during exercise is reduced for each given workload compared with that in normal people.[1] The oxygen consumption of exercising skeletal muscle at each level of work is lower in patients with chronic heart failure and is accompanied by an early increase in plasma lactate concentration.[1] The reduced maximal blood flow to working muscle during exercise occurs predominantly in oxidative working muscle.[2]

What causes impaired metabolic vasodilatation in heart failure?

The impaired metabolic vasodilatory capacity of skeletal muscle in patients with chronic heart failure during exercise is often attributed to excessive sympathetic vasoconstriction, activation of the plasma renin-angiotensin system, and, more recently, to increased concentrations of endothelin.[3] Endothelin has an important role in the pulmonary circulation,[4] but its pathophysiological relevance in the systematic circulation in chronic heart failure remains to be established.

Although the activated sympathetic and renin-angiotensin systems exert potent systemic and regional vasoconstriction, they do not completely explain the impaired vasodilatation in skeletal muscle in patients with chronic heart failure. Impaired metabolic vasodilatation during exercise cannot be restored by α blockade with phentolamine.[5 6] Similarly, short term treatment with angiotensin converting enzyme (ACE) inhibitors does not restore impaired metabolic vasodilatation, despite a substantial reduction in plasma angiotensin II and noradrenaline concentrations.[7] This indicates that blockade of the plasma renin-angiotensin system by ACE inhibitors does not interfere with blood flow to working muscle during exercise in patients with congestive heart failure.[7 8] Treatment with an ACE inhibitor over several months, however, causes a significant increase in femoral blood flow during exercise and improves peak oxygen consumption.[7] Thus, long term ACE inhibition reverses, at least in part, the inability of peripheral vessels to dilate. These findings are consistent with the previous observation that the beneficial effect of ACE inhibition in large scale trials is delayed,[9] indicating that the full effect of ACE inhibitors emerges only slowly over time. Similarly, the restoration of peripheral perfusion and skeletal muscle function takes weeks or months after cardiac transplantation.

Several factors have been proposed to explain the delayed beneficial effects of ACE inhibitors on peripheral perfusion. The delayed effect of ACE inhibitors may be due, in part, to reversal of long term structural changes in resistance vessels. Activation of the renin-angiotensin system in vascular tissue may be particularly important in bringing about changes in vascular structure. Data from our laboratory, however, indicate that tissue ACE activity is not raised in the aorta and skeletal muscle of rats with induced heart failure.[10] Moreover, results from experimental and clinical studies investigating structural alterations of resistance vessels in chronic heart failure are scarce and contradictory.

Endothelial dysfunction in heart failure

Whereas it remains controversial whether structural changes occur in the microcirculation of skeletal muscle, flow dependent dilatation and dilatation of large conduit vessels induced by glyceryl trinitrate are impaired in patients with heart failure. This suggests that relaxation of vascular smooth muscle in large conduit vessels is impaired.[11] This may have functional consequences since it impairs the elastic properties of the conduit vessels, increases aortic impedance, and has an adverse effect on left ventricular systolic performance. There is preliminary evidence that endothelium derived relaxing factor (EDRF) dynamically controls large artery distensibility, suggesting a physiological role for the factor in reducing cardiac work relative to tissue perfusion.[12] Although, the compliance of large arteries is impaired in patients with chronic heart failure,[13] the role of endothelial dysfunction in this context remains to be elucidated.

Tissue perfusion is primarily regulated by the resistance vessels. The pivotal role of EDRF in determining not only vascular tone of conduit vessels but also tone of resistance vessels and therefore tissue perfusion is now recognised. Firstly, nitric oxide accounts for most or all of the biological activity of EDRF[14] and is continuously released from the endothelium, providing a constant counteracting force to vasoconstrictor substances such as noradrenaline and angiotensin II. Secondly, EDRF can be released from the endothelium on stimulation—that is, by bradykinin or ADP.

Medizinische Klinik III, University of Freiburg, Freiburg, Germany
H Drexler

Correspondence to:
Dr H Drexler,
Medizinische Klinik III,
University of Freiburg,
Hugstetterstrasse 55,
79106 Freiburg, Germany.

Several pathophysiological conditions such as hypercholesterolaemia and hypertension are associated with dysfunctional endothelium—that is, either the basal or the stimulated release of EDRF is altered. Our data and those of Kubo *et al* have shown that endothelium dependent relaxation of the skeletal muscle microcirculation in response to acetylcholine is impaired in chronic heart failure, whereas the vasodilating effect of glyceryl trinitrate is preserved in compensated heart failure.[15–17] Although the functional importance of this finding remains to be established, endothelial dysfunction in the peripheral circulation is probably part of the impaired reactive hyperaemia to exercise or ischaemia in heart failure. In the coronary circulation also, inhibition of the synthesis of nitric oxide reduces reactive hyperaemia.

The basal release of nitric oxide contributes to the control of regional blood flow in humans by using N-monomethyl-L-arginine (L-NMMA), a selective inhibitor of nitric oxide production from L-arginine.[18] In the absence of marked vasoconstriction of conduit vessels, changes in blood flow reflect the response of resistance vessels. To identify the endothelium dependent vasomotor response of large forearm conduit and small resistance vessels we used a new ultrasound device to accurately determine forearm arterial diameter.[19 20] Simultaneously, blood flow velocity in the same vessel was recorded by a Doppler velocity device. By this approach, the effects of intra-arterial infusion of acetylcholine, L-NMMA, and glycerol trinitrate on forearm conduit and resistance vessels were examined in patients with chronic congenital heart failure and in age matched healthy volunteers.

Whereas the blood flow response to acetylcholine was blunted in heart failure, the decrease in flow induced by L-NMMA was enhanced and the response to glyceryl trinitrate was preserved.[16] Since L-NMMA inhibits the basal release of nitric oxide, an exaggerated vasoconstrictor response in heart failure (as compared with normal subjects) is consistent with the notion that the basal release of nitric oxide is increased in the peripheral circulation of patients with heart failure. By contrast, endothelium dependent dilatation of forearm resistance vessels by acetylcholine is impaired in heart failure, suggesting a defect distal to muscarinic receptors. Since the dilator response to both acetylcholine and glyceryl trinitrate entails activation of the guanylate cyclase system, a generalised defect within this system cannot account for the present finding.

In conclusion, impaired vasodilatation, at least in milder degrees of heart failure, seems to be selective rather than generalised, possibly at the receptor level, and stimulated and basal release of nitric oxide are dissociated in patients with heart failure. In more severe heart failure the general impaired vasodilator response may be due to defects in guanylate cyclase or structural alterations in the vasculature.

The observation that a substantial reduction in forearm blood flow occurred with L-NMMA in the absence of significant changes in diameter of large conductance vessels suggests a preferential release or activity of nitric oxide in forearm resistance vessels as compared with large conductance vessels in humans. Thus, the basal release of nitric oxide seems to have an important role in modulating tissue perfusion at the levels of distal resistance vessels in the forearm in heart failure, but it may be less prominent in conduit vessels. Alternatively, its effect on vasomotor tone in large arteries is overridden by other factors.

Interestingly, Teerlink *et al* have found that endothelial dysfunction in heart failure is a progressive time dependent process.[21] Since haemodynamic compromise was documented at a time when endothelial dysfunction was absent, these findings suggest that endothelial dysfunction in chronic heart failure is not merely the direct result of impaired cardiac output and left ventricular dysfunction.

The vasomotor response to acetylcholine in patients with heart failure cannot be attributed solely to the release of EDRF. Release of a cyclo-oxygenase dependent vasoconstrictor substance by acetylcholine has been reported in the femoral artery of dogs with induced heart failure[22] and, more recently, in patients with chronic heart failure.[23]

In patients with severe heart failure the vasodilator response to glyceryl trinitrate is reduced,[23] suggesting a decreased responsiveness of vascular smooth muscle to vasodilators mediated by cyclic GMP. Although there are conflicting data concerning the regional vasodilator response to nitrates in patients with heart failure, the controversy may be reconciled by acknowledging the different patient populations studied. In compensated heart failure the response to glyceryl trinitrate is usually preserved, whereas in severe cases, particularly when oedema has developed, the vasodilator response to the nitrate or to sodium nitroprusside is impaired. A potential mechanism for impaired nitrate induced peripheral dilatation in chronic heart failure is increased vascular stiffness due to increased vascular sodium content, which can be, in part, reduced with diuretic treatment in decompensated heart failure.[24]

Regional vascular vasoconstrictor mechanisms in chronic heart failure limiting blood flow during exercise

Mechanism
Sympathetically mediated vasoconstriction
Activated renin-angiotensin system in plasma and vascular tissue
Enhanced vascular stiffness—for example, due to increased sodium content of vessel wall
Blunted stimulated release of EDRF in resistance vessels (limited endothelium dependent dilatation), impaired flow dependent dilatation
Possible structural vascular changes—for example, from stimulated growth by angiotensin II and noradrenaline and long term reduced flow

EDRF, endothelium derived relaxing factor.

Reversal of peripheral endothelial dysfunction by ACE inhibitors

Long term ACE inhibition improves skeletal muscle blood flow and oxygen extraction during exercise.[7] Conceivably, ACE inhibitors improve skeletal muscle flow by reversing endothelial dysfunction. Indeed, experimental evidence suggests that long term treatment with ACE inhibitors improves aortic endothelial dysfunction in experimental heart failure[25] and in hypertensive rats.[26]

The beneficial effect of ACE inhibitors on endothelial function might be due to the inhibition of the breakdown of bradykinin, which is normally degraded by ACE.[27] Inhibition of ACE may increase local tissue concentrations of bradykinin, which, in turn, stimulate the release of nitric oxide (which accounts for the biological activity of EDRF) and vasodilating prostaglandins.[27 28] This pathway may also have important long term effects as nitric oxide may inhibit mitogenesis and proliferation of vascular smooth muscle cells. Moreover, both nitric oxide and prostaglandins affect flow dependent dilatation, which, in turn, may improve large conduit vessel function and tissue perfusion.

Preliminary data suggest that ACE activity (including ACE messenger RNA) and endothelial function are inversely related in the aorta of hypertensive rats.[29] ACE inhibitors were able to restore endothelial function and inhibited aortic ACE activity. Importantly, concomitant treatment with an ACE inhibitor and a bradykinin antagonist did not improve endothelial dysfunction. These observations suggest that in rats the beneficial effect of ACE inhibition is provided by an increased availability of bradykinin.[30]

Whereas the presence, if not the nature, of endothelial dysfunction is well documented in patients with chronic heart failure, the impact of ACE inhibition on endothelial function remains to be determined. Preliminary data suggest that the increase in forearm blood flow elicited by acute administration of enalapril is mediated by prostaglandins since the effect of enalapril was reduced after pretreatment with indomethacin or aspirin[31 32]; the contribution of bradykinin and nitric oxide remains uncertain.

One clinical study reported that short term treatment with captopril improves impaired acetylcholine induced endothelium dependent vasodilatation in hypertensive patients.[33] This is perhaps surprising since acetylcholine induced vasodilatation is independent of bradykinin.

Based on current experimental findings, the beneficial effect of ACE inhibitors on endothelial function can be best explained by their interference with the breakdown of bradykinin, which, in turn, stimulates the release of nitric oxide and prostaglandins. The significance of this short term effect of captopril on endothelial function in the long term treatment of hypertension awaits clinical trials of long term ACE inhibition. Preliminary data from our laboratory suggest that taking ACE inhibitors for three months may improve forearm vascular function in patients with chronic heart failure who are not being treated with aspirin.[34]

The contribution of the bradykinin-prostaglandin pathway may, however, vary in different circulatory beds. For example, earlier studies in humans have shown that inhibition of the kallikrein-kinin system does not affect the captopril induced increase in renal plasma flow, despite the suppression of plasma bradykinin concentrations.[35]

HD is supported in part by the Deutsche Forschungsgemeinschaft (Dr 148/6-1, 7-1).

1 Zelis R, Longhurst J, Capone RJ, Mason DT. A comparison of regional blood flow and oxygen utilization during dynamic forearm exercise in normal subjects and patients with congestive heart failure. *Circulation* 1974;**50**:137–43.

2 Drexler H, Faude F, Höing S, Just H. Blood flow distribution within skeletal muscle during exercise in the presence of chronic heart failure: effect of milrinone. *Circulation* 1987;**76**:1344–52.

3 McMurray JJ, Ray SG, Abdullah I, Dargie HJ, Morton JJ. Plasma endothelin in chronic heart failure. *Circulation* 1992;**85**:1374–9.

4 Giaid A, Yanagisawa M, Langleben D, *et al.* Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993;**328**:1732–9.

5 Zelis R, Mason DT, Braunwald E. A comparison of the effects of vasodilator stimuli on peripheral resistance vessels in normal subjects and patients with congestive heart failure. *J Clin Invest* 1968;**47**:960–70.

6 LeJemtel TH, Maskin CS, Lucido D, Chadwick BJ. Failure to augment maximal limb blood flow in response to one leg versus two-leg exercise in patients with severe heart failure. *Circulation* 1986; **74**:245–51.

7 Drexler H, Banhardt U, Meinertz T, Wollschläger H, Lehmann M, Just H. Contrasting peripheral short-term and long-term effects of converting enzyme inhibition in patients with congestive heart failure. A double-blind, placebo-controlled trial. *Circulation* 1989;**79**:491–502.

8 Wilson JR, Ferraro N. Effect of renin-angiotensin system on limb circulation and metabolism during exercise in patients with heart failure. *J Am Coll Cardiol* 1985;**6**: 556–63.

9 Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol* 1983;**2**: 755–63.

10 Schieffer B, Wirger A, Meybrunn M, *et al.* Comparative effects of chronic ACE-inhibition and AT1 receptor blockade on cardiac remodelling after myocardial infarction in the rat. *Circulation* 1994;**89**:2273–82.

11 Hayoz D, Drexler H, Münzel T, *et al.* Flow-mediated arterial dilation is abnormal in congestive heart failure. *Circulation* 1993;**87**:VII-92–6.

12 Ramsey MW, Jones CJH, Stewart W, Lewis MJ, Henderson AH. Endothelium-derived relaxing factor dynamically controls large artery distensibility in normal subjects [abstract]. *Eur Heart J* 1993;**14**:274.

13 Arnold JMO, Marchiori GE, Imrie JR, Burton GL, Pflugfelder PW, Kostuk WJ. Large artery function in patients with chronic heart failure. Studies of brachial artery diameter and hemodynamics. *Circulation* 1991; **84**:2418–25.

14 Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987;**327**:524–6.

15 Drexler H, Lu W. Endothelial dysfunction of hindquarter resistance vessels in experimental heart failure. *Am J Physiol* 1992;**262**:H1640–5.

16 Drexler H, Hayoz D, Münzel T, *et al.* Endothelial function in chronic congestive heart failure. *Am J Cardiol* 1992;**69**:1596–601.

17 Kubo SH, Rector TS, Bank AJ, Williams RE, Heifetz SM. Endothelium-dependent vasodilation is attenuated in patients with heart failure. *Circulation* 1991;**84**:1589–96.

18 Vallance P, Collier J, Moncada S. Effects of endothelium-derived nitric oxide on peripheral arteriolar tone in man. *Lancet* 1989;ii:997–1000.

19 Tardy Y, Meister JJ, Perret F, Brunner HR, Arditi M. Non-invasive estimate of the mechanical properties of peripheral arteries from ultrasonic and photoplethysmographic measurements. *Clin Phys Physiol Meas* 1991;**12**:39–54.

20 Perret F, Mooser V, Hayoz D, *et al.* Evaluation of arterial compliance-pressure curves: effect of antihypertensive drugs. *Hypertension* 1991;**18**:II-77–83

21 Teerlink JR, Clozel M, Fischli W, Clozel JP. Temporal evolution of endothelial dysfunction in a rat model of chronic heart failure. *J Am Coll Cardiol* 1993;**22**: 615–20.

22 Kaiser L, Spickard RC, Olivier NB. Heart failure depresses endothelium-dependent responses in canine femoral artery. *Am J Physiol* 1989;**256**:H962–7.

23 Katz SD, Schwartz M, Yuen J, LeJemtel TH. Impaired acetylcholine-mediated vasodilatation in patients with congestive heart failure. Role of endothelium-derived vasodilating and vasoconstricting factors. *Circulation* 1993;**88**:55–61.
24 Sinoway LI, Minotti J, Musch T, *et al.* Enhanced metabolic vasodilatation secondary to diuretic therapy in decompensated congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1987;**60**:107–11.
25 Lindsay DC, Jiang C, Brunnotte F, *et al.* Impairment of endothelium-dependent responses in a rat model of chronic heart failure: effects of an exercise training protocol. *Cardiovasc Res* 1992;**26**:694–7.
26 Clozel M, Kuhn H, Hefti F. Effects of angiotensin converting enzyme inhibitors and of hydralazine on endothelial function in hypertensive rats. *Hypertension* 1991;**16**:532–40.
27 Mombouli J-V, Naphtali M, Vanhoutte PM. Effects of the converting enzyme inhibitor cilazaprilat on endothelium-dependent responses. *Hypertension* 1991;**18**(suppl II): 22–9.
28 Wiemer G, Schölkens BA, Becker RHA, Busse R. Ramiprilat enhances endothelial autacoid formation by inhibiting breakdown of endothelium-derived bradykinin. *Hypertension* 1991;**18**:558–63.
29 Goetz RM, Studer R, Reinecke H, Holtz J. Enhanced gene expression of angiotensin converting enzyme accounts for endothelial dilatory dysfunction in aorta of rats with coarctation hypertension. *Eur Heart J* 1993; **14**(suppl):347.
30 Goetz RM, Krivokuca M, Holtz J. Local activity of angiotensin converting enzyme and local endothelium-dependent dilatory reactivity in coarctation hypertension. *Circulation* 1992;**86**:I–558.
31 Hirsch H, Bijou R, Yuen J, Katz S, Sonnenblick EH, LeJemtel TH. Enalapril-mediated vasodilation is attenuated by indomethacin in congestive heart failure and completely abolished in normal subjects. *Circulation* 1993;**88**:I–293.
32 Funakoshi T, Nakamura M, Chiba M, *et al.* Effects of ACE-inhibition on endothelium-dependent vasodilation in patients with chronic heart failure. *Circulation* 1993;**88**:I–293.
33 Hirooka Y, Imaizumi T, Masaki H, *et al.* Captopril improves impaired endothelium-dependent vasodilatation in hypertensive patients. *Hypertension* 1992;**20**: 175–80.
34 Jeserich M, Pape L, Münzel T, Kupfer M, Drexler H, Just H. Longterm ACE inhibition improves vascular function in patients with chronic heart failure by a cyclooxygenase dependent mechanism [abstract]. *JACC* 1994: 273A.
35 Kubo S, Nishioka A, Nishimura H, Kawamura K, Takatsu T. Effects of converting-enzyme inhibition on cardiorenal hemodynamics in patients with chronic heart failure. *J Cardiovasc Pharmacol* 1985;7:753–9.